

REMARKS

I. Status Summary

Claims 23-30 and 32-46 are pending in the present application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office"). Applicants note with gratitude that the finality of the previous Official Action has been withdrawn and the amendment of October 21, 2008 has been entered.

Claims 23-30 and 32-46 have been rejected on one or more bases under 35 U.S.C. § 112, second paragraph, upon the contention that the claims are indefinite.

Claims 23, 24, 27-30, 32-34, 37, 40, 41, 43, and 44 have been rejected under 35 U.S.C. § 102(e) upon the contention that they are anticipated by U.S. Patent No. 6,458,585 to Vachula et al. (hereinafter "Vachula").

Claims 23, 24, 26-30, 32-35, 37, 40, 41, 43, and 44 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Vachula. Claims 23-30, 32-41, and 43-46 have been rejected under this section upon the contention that the claims are unpatentable over Vachula and further in view of U.S. Patent No. 5,853,719 to Nair et al. (hereinafter "Nair"). Claims 23-30 and 32-46 have also been rejected under this section upon the contention that the claims are unpatentable over Vachula and Nair and further in view of U.S. Patent No. 6,077,519 to Storkus et al. (hereinafter "Storkus") and PCT International Patent Application Publication No. WO 98/58956 of Warnier et al. (hereinafter "Warnier").

Claims 23, 24, 27-29, 33, 35, 38, and 40-42 have been amended to address the alleged ambiguities under 35 U.S.C. § 112, second paragraph, and/or to correct typographical errors. Support for these amendments is found throughout the original application and more specifically as indicated hereinbelow for each amendment. Accordingly, applicants respectfully submit that no new matter has been introduced by the amendments to the claims.

Reconsideration of the application in view of the remarks set forth herein is respectfully requested.

II. Responses to the Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 23-30 and 32-46 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In an effort to facilitate prosecution and without acquiescing to the contentions of the Patent Office, certain claims have been amended to address the ambiguities asserted by the Patent Office.

Claims 23, 27, 28, 33, and 38 are allegedly vague and indefinite in the recitation of “proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells.” Claims 23, 27, and 33 have been amended to reposition “overexpressed in tumor cells...” such that this modifier refers to the origin of the proteins and/or peptides or RNA or DNA or cDNA selected. Support for these amendments is found in paragraphs 30-31 of the specification as well as in the “Flow Chart for Preparation of cRNA” beginning at paragraph 64. The same phrase has been removed altogether from Claims 28 and 38, which depend from Claims 27 and 23, respectively. Support for this amendment is found in the base claims.

Claims 29 and 41 are allegedly vague and indefinite in the recitation of “proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides from several different tumor cell lines.” Claim 29 has been amended to remove the element of antigen-presenting cells repeated from the base claim. Support for this amendment is found in Claim 27, the base claim.

Claim 41 has been amended to remove elements repeated from Claim 33, the base claim, and to clarify the origin of the proteins and/or peptides. Support for this amendment is found in the original claim as well as in the base claim. Claim 41 is also allegedly vague and indefinite in recitation of “introduced for the treatment of tumor diseases in said patient.” The Patent Office further objects to inclusion of the intended use of the cells in the claim. Claim 41 has been amended, and the contentions of the Patent Office are believed to be rendered moot. Support for this amendment is found in the original claim as well as paragraphs 35, 60, and 65 of the specification.

Claim 24 is allegedly vague and indefinite due to the allegedly unclear placement of the modifier “peptides from several different tumor cell lines.” Claim 24 has been amended to remove an element repeated from the base claim. Any alleged ambiguity is

believed to be alleviated by repositioning the modifier to indicate that it refers to the source of the proteins and/or peptides. Support for this amendment is found in Claim 23, the base claim.

Claim 42 is allegedly vague and indefinite for allegedly failing to provide an object into which the cell lines are introduced. Claim 42 has been amended, and the contentions of the Patent Office are believed to be rendered moot. Support for this amendment is found in the base claim (41) and *inter alia* at paragraph 17.

Claims 25, 26, 39, 45, and 46 depend directly or indirectly from Claim 23 and are believed to be in proper form after the amendment to the base claim. Claims 30 and 32 depend from Claim 27 and are believed to be in proper form after the amendment to the base claim. Claims 34-37 and 44 depend directly or indirectly from Claim 33 and are believed to be in proper form after the amendment to the base claim. Claim 43 depends from Claim 28 and is believed to be proper following amendment of the base claim.

Applicants respectfully submit that the instant rejection is believed to have been addressed and request that it be withdrawn at this time. Allowance of the pending claims is also respectfully requested.

III. Response to the Rejection under 35 U.S.C. § 102(e)

Claims 23, 24, 27-30, 32-34, 37, 40, 41, 43, and 44 have been rejected under 35 U.S.C. § 102(e) upon the contention that they are anticipated by Vachula. According to the Patent Office, Vachula discloses a method of making loaded dendritic cells by pulsing with antigen and use of the antigens to produce antigen-specific dendritic cells for treatments against various carcinomas and melanoma. Vachula also allegedly discloses washing, concentration of antigen pulsed dendritic cells, followed by IV-infusion directly into a patient as a type of vaccine against tumor cells. Finally, Vachula is asserted to disclose that ideally the donor and recipient will be completely HLA matched, as may occur fortuitously among full siblings. The Patent Office asserts that this latter disclosure “fulfill(s) the specific embodiment of... haploidentical with respect to ‘completely HLA-matched.’” Official Action, p. 4.

After careful consideration of the rejection and the Patent Office’s basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that Vachula does not disclose or suggest the use of HLA-haploidentical antigen presenting cells (APCs). Applicants respectfully submit that Vachula is directed entirely towards employing HLA-matched APCs, which are not HLA-haploidentical but *fully* HLA-identical.

To elaborate on and further illustrate this concept, two different black-and-white diagrams of the same family are enclosed, submitted as Exhibits A and B. Exhibit A, labeled “HLA-matched Donors,” shows one individual, designated “Sibling 1,” who shares both chromosomes with “P” and therefore may donate cells to patient “P” according to the method of Vachula. In this depiction of the pedigree, both Sibling 1 and patient “P” have the chromosomes HLA-a and HLA-c and are therefore “HLA-matched” or fully HLA-identical.

Exhibit B, labeled “HLA-Haploidentical Donors,” shows in contrast that a number of different individuals from the same family (but *not* the HLA-matched Donor, Sibling 1, noted above) are suitable donors to provide cells for “P” according to the method of the present invention. A donor who is “HLA-haploidentical” shares only one HLA-haplotype with the patient “P.”

The mixture of cells from two HLA-haploidentical donors can include cells donated by Sibling 2 and Sibling 3. Together they provide matches with patient “P” for both HLA haplotypes, but each cell has one non-matched HLA haplotype as well. The non-matched chromosome from each donor leads to activation of allogenic T cells and NK cells in recipient patient “P.” As such, Sibling 1 is not a suitable donor with respect to the presently claimed methods, because he does not have any mismatched HLA-haplotypes. “HLA-haploidentical” is used interchangeably with “semi-allogenic HLA-haploidentical” in the present application. Thus, the “HLA-matched donors” of Vachula and “HLA-haploidentical donors” of the presently disclosed and claimed subject matter are significantly different.

Applicants respectfully note that Figure 2 of the application as originally filed illustrates the same concept as described in Exhibits A and B enclosed. The Patient in Figure 2 has HLA-ac, while the father/donor has HLA-ab and the mother/donor has HLA-cd. Thus, in this example each cell donor has one chromosome that matches a

patient HLA haplotype *and one that does not match*, also noted in Paragraph 63 of the instant application.

Stated another way, independent claims 23, 27, and 33 all recite *inter alia* that the antigen-presenting cells (APCs) are “HLA-haploidentical” with respect to those of the patient. Thus, HLA-haploidentical cells are not believed to be HLA-matched cells. Applicants respectfully note that all of the instant independent claims are drawn to use of semi-allogenic HLA-haploidentical cells.

Since Vachula is asserted to disclose the use of “HLA-matched” dendritic cells, applicants respectfully submit that Vachula does not support a rejection of claims 23, 27, and 33 under 35 U.S.C. § 102(e). Claims 24, 28-30, 32, 34, 37, 40, 41, 43 and 44 all depend directly or indirectly from claim 23, 27, or 33, and thus are also believed to be distinguished over the cited reference. Therefore, applicants respectfully submit that Vachula lacks a disclosure of haploidentical APCs, and therefore the Patent Office has not provided a *prima facie* case of obviousness of claims 23, 24, 27-30, 32-34, 37, 40, 41, 43, and 44 over Vachula.

Accordingly, applicants respectfully request that the instant rejection of claims 23, 24, 27-30, 32-34, 37, 40, 41, 43, and 44 under 35 U.S.C. § 102(e) over Vachula be withdrawn at this time.

#### IV. Responses to the Obviousness Rejections

Claims 23, 24, 26-30, 32-35, 37, 40, 41, 43, and 44 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Vachula. Claims 23-30, 32-41, and 43-46 have been rejected under this section upon the contention that the claims are unpatentable over Vachula and further in view of Nair. Claims 23-30 and 32-46 have also been rejected under this section upon the contention that the claims are unpatentable over Vachula and Nair and further in view of Storkus and Warnier.

After careful consideration of the rejection and the Patent Office’s basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

IV.A. Response to the Rejection over Vachula

Claims 23, 24, 26-30, 32-35, 37, 40, 41, 43, and 44 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Vachula. The Patent Office concedes that Vachula does not specifically teach using two completely HLA-matched dendritic cell donors. However, the Patent Office asserts that while Vachula teaches the use of APC from only one HLA-matched dendritic cell donor, it would have been *prima facie* obvious to use “two different completely HLA-matched donors,” in the event that only one donor is insufficient. Applicants respectfully submit that this assertion apparently relies on the misunderstanding of the distinction between “HLA-matched donors” and “HLA-haploidentical donors,” as addressed in the paragraphs above. Applicants emphasize that the instant subject matter does not utilize cells from completely HLA-matched donors.

As such, applicants respectfully submit that it is only by using impermissible hindsight reasoning using applicants’ own disclosure that the Patent Office can conclude that one of ordinary skill in the art would think to employ HLA-haploidentical APCs. As set forth in M.P.E.P. § 2142, “impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art” (emphasis added). Given that none of the references cited by the Patent Office mentions the use of HLA-haploidentical APCs, the only disclosure relating to this particular source of APCs is applicants’ specification. Since applicants’ specification cannot provide the motivation for combining references, applicants respectfully submit that the instant rejection is believed to be improperly based on hindsight.

Summarily, in the instant rejection, the Patent Office has provided no basis independent of applicants’ disclosure for concluding that one of ordinary skill in the art would have been motivated to employ HLA-haploidentical APCs. Therefore, applicants respectfully submit that the instant rejection is not a case where the Patent Office has only taken into account knowledge asserted to be within the level of one of ordinary skill in the art at the time the claimed invention was made. Rather, the use of applicants’ specification to provide the motivation to combine the references is improper, and thus the Patent Office has failed to establish a *prima facie* case of obviousness of claims 23, 24, 26-30, 32-35, 37, 40, 41, 43, and 44 over Vachula.

Accordingly, applicants respectfully submit that the instant obviousness rejection of 23, 24, 26-30, 32-35, 37, 40, 41, 43, and 44 under 35 U.S.C. § 103(a) over Vachula is believed to be improper, and respectfully request that it be withdrawn at this time.

IV.B. Response to the Rejection over Vachula in view of Nair

Claims 23-30, 32-41, and 43-46 have also been rejected under 35 U.S.C. § 103(a) upon the contention that they are unpatentable over Vachula and in further view of Nair. According to the Patent Office, the combination of Vachula and Nair render obvious the instant invention regarding the use of cDNA reverse transcription and amplification as a recombinant source of peptides or proteins, elements missing from Vachula. The Patent Office also asserts that it would have been *prima facie* obvious to substitute RNA or cDNA transfection for the peptide pulsing and to utilize unfractionated RNA or cDNA according to Nair.

Applicants respectfully disagree. M.P.E.P. § 2142 cites the decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. \_\_\_, 82 USPQ2d 1385 (2007) of the Court of Appeals for the Federal Circuit (hereinafter the “Federal Circuit”) for the proposition that “rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness’ (emphases added).” *KSR*, 550 U.S. at \_\_\_, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). The Patent Office’s assertions with respect to substituting RNA or cDNA transfection for peptide pulsing and using unfractionated RNA or cDNA do not satisfy this requirement as there has been no articulated basis for concluding that upon consideration of the Vachula reference, one of ordinary skill in the art would have been motivated to consult Nair regarding the use of unfractionated RNA or cDNA, let alone with HLA-haploidentical APCs.

The HLA-haplotype of the APCs is not addressed by Nair. In particular, applicants respectfully submit that there is no disclosure in either Vachula or Nair that teaches or suggests the use of HLA-haploidentical APCs. Thus, applicants respectfully submit that the combination of Vachula and Nair does *not* cure the Vachula deficiency with regard to HLA-haploidentical APCs. Therefore, the combination does not render

obvious the instant subject matter regarding the loading of HLA-haploidentical APCs with unfractionated RNA or cDNA made from patient tumor tissue.

Accordingly, applicants respectfully submit that the instant obviousness rejection of Claims 23-30, 32-41, and 43-46 over Vachula in view of Nair is believed to be improper, and respectfully request that it be withdrawn at this time.

IV.C. Response to the Rejection over Vachula and Nair in view of Storkus and Warnier

Claims 23-30 and 32-46 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Vachula and Nair and further in view of Storkus and Warnier. The Patent Office asserts that Storkus teaches cDNA transfection of dendritic cells as an alternative to peptide pulsing, administration of pulsed dendritic cells by intravenous routes, applications to various carcinomas, and the use of cDNA from multiple tumor cell lines. According to the Patent Office, “it would have been *prima facie* obvious to use pooled tumor cell acid eluted peptides or RNA or cDNA for pulsing or loading the dendritic cells used in the methods rendered obvious by the combination” of Vachula and Nair. The Patent Office also asserts that the teachings of Warnier regarding expression of tumor antigens support the goal of having APCs express polytopes, comprising multiple epitopes on tumor antigens. Again, the Patent Office states no articulated basis for concluding that upon consideration of the Vachula reference (or Vachula in combination with Nair), one of ordinary skill in the art would have been motivated to consult either Storkus or Warnier.

Furthermore, this assertion fails to acknowledge the element of HLA-haploidentical APCs in the instant claims. Applicants respectfully submit that neither Storkus nor Warnier cure this deficiency. Storkus teaches using “autologous” or “HLA-matched” dendritic cells (column 5, lines 19-20 and column 6, lines 15-17). Again, “HLA-matched” does not mean “HLA-haploidentical,” as detailed above with respect to Vachula. Warnier also refers to “autologous dendritic cells” which are believed to be completely HLA-matched (p. 3, line 7). Thus applicants respectfully submit that the element of HLA-haploidentical APCs is not disclosed in Vachula, nor does combination with Nair or Storkus and Warnier cure the deficiency.

Accordingly, applicants respectfully submit that the instant obviousness rejection of Claims 23-30 and 32-46 over Vachula and Nair in view of Storkus and Warnier is believed to be improper, and respectfully request that it be withdrawn at this time. Applicants further respectfully submit that claims 23-30 and 32-46 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above, it is respectfully submitted that the present application is now in proper condition for allowance, and a Notice of Allowance to that effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

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By:



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